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Review

Kainate receptor pharmacology and physiology

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Abstract. Glutamate is the primary neurotransmitter in the central nervous system. One of the classes of ionotropic glutamate receptors is kainate receptors. Recent developments in the pharmacology of kainate receptors have resulted in the emergence of several selective agonists and antagonists. These compounds have allowed scientists to begin to probe the functional properties of these receptors in neurons and gain a better understanding of the role of these receptors in the nervous system.

Key words. Glutamate receptors; antagonist; desensitization; agonist.

Historical perspectives

The action of glutamate as an excitatory neurotransmitter was first described by Hayashi [1, 2] and Curtis and colleagues [3]. The observation that glutamate could depolarize neurons suggested that this molecule had potential as a neurotransmitter. However, the notion that an amino acid, present at relatively high concentration in the central nervous system, could be responsible for the majority of neurotransmission only gained acceptance upon later evidence from pharmacological, electrophysiological and, more recently, molecular biological studies.

The existence of subtypes of receptors for glutamate was advanced by the observations that glutamate agonist analogues such as *N*-methyl-D-aspartate (NMDA), quisqualate and kainate showed different potencies on subsets of neurons [4, 5]. In addition, several antagonists emerged that had differential effects on these agonist responses [e.g. D-α-aminoadipate (GAMS), magnesium ions, kynurinic acid and glutamate diethyl ester] [6–9]. Hence, an initial classification of NMDA, quisqualate and kainate receptors arose [9]. Since quisqualate was shown to activate metabotropic glutamate receptors [10, 11] and a new agonist, AMPA [12], appeared to be a more selective agent for the quisqualate activated non-NMDA receptors, the ionotropic glutamate receptor family was reclassified as NMDA, AMPA and kainate [13]. Molecular biology has since resulted in the cloning and functional expression of a variety of NMDA, AMPA and kainate receptor subunits [14].

Molecular cloning of kainate receptors

To date five kainate receptor subunits have been cloned (rat and human) [15–29]. These kainate receptor subunits comprise approximately 900 amino acids (M_r of approximately 100 kDa) and have approximately 40% sequence homology with AMPA receptor subunits GluR1–4. Two of these subunit proteins (KA1 and KA2) show high affinity for ^{3}H kainate binding. They share about 70% sequence homology and, when expressed in host cells, do not appear to form functional ion channels. The three other kainate receptor types, GluR5, GluR6 and GluR7, have lower affinity for ^{3}H kainate binding than KA1 and KA2 subunits but have affinity that is comparable to high-affinity binding sites measured in rat brain homogenates [30, 31]. In contrast

to KA1 and KA2, GluR5, GluR6 and GluR7 can form functional ion channels when expressed homomerically. KA1 and KA2 subunits are also able to form heteromeric assemblies with GluR5 and GluR6 kainate receptors [32].

For rat kainate receptors, GluR5 and GluR7 have been demonstrated to exist as alternatively spliced forms. For GluR5, there are GluR5-1 and GluR5-2 variants [15]. These variants differ by virtue of the absence or presence of an exon encoding a 15-amino acid sequence in the N-terminal domain. For GluR5-2 there are also GluR5a, b and c splice variants that differ in c-terminal sequences [24]. Human GluR5 also exists in alternatively spliced forms, a GluR5-1d [25] and EAA3a [33]. A mouse GluR6 splice variant GluR6-2 has also been reported [25]. For GluR7 there are also two alternatively spliced forms of the receptor GluR7 a and b [34].

Posttranslational editing of GluR5 and GluR6 (but not GluR7) subunits can occur in a similar manner to that observed with AMPA receptors [35]. Thus, RNA editing of glutamine (Q) to arginine (R) in the pore region (TMII) of the receptor subunit results in distinct functional consequences [36]. GluR7, KA1 and KA2 possess a glutamine (Q) residue at this editing site [32]. Homomeric GluR5(R) and GluR6(R) appear to form functional ion channels with subpicosiemen conductances, whereas GluR5(Q), and GluR6(Q) and heteromerics with KA2, form ion channels with much larger ion conductances [37]. The unedited forms of GluR6(R) kainate receptors show a calcium permeability (a feature of Q/R editing) considerably lower than GluR5(Q) [38] (see below). Additional isoforms of GluR6 have been demonstrated with editing of isoleucine (I–V) to valine and cysteine to tyrosine (Y to C) in the TMI region of the receptor [39, 40], an effect shown to lower the calcium permeability of the channels. Editing of GluR5 (35%) and GluR6 (75%) [36] appears less efficient than that seen with GluR2 and appears to be developmentally regulated. For example, nominal editing of GluR5 and 6 occurs during embryonic development, whereas in adults, editing of GluR5 and GluR6 is more substantial (50 and 70–90%, respectively). For editing of GluR6 in the transmembrane region I (TMI), it would appear that the GluR6 (R/V/C) isoform predominates in adults [40].

Kainate receptor properties

Several approaches have been used to identify the subtype(s) of kainate receptors associated with an observed neuronal kainate receptor response. Such approaches include mapping the distribution of receptors, examining the biophysical properties of kainate responses and finally a pharmacological analysis of the effects of selective agonists and antagonists.

With respect to native kainate receptors, wide distributions of (messenger RNA) mRNA of kainate receptor subunits have been observed in the central nervous system (CNS) [15, 17, 21, 41], including regions such as the cerebellum, amygdala, hippocampus and spinal cord. In addition, kainate receptor transcripts appear to be developmentally regulated with subunit gene distribution changing markedly between an early postnatal stage of development and the adult [42]. The absence of subunit specific antibodies for kainate receptors has increased the challenge to interpretations of expressed protein distributions. However, recent single-cell polymerase chain reaction (PCR)/whole cell patch-clamp studies performed on neurons have given clues to the absence or presence of mRNA, not only for specific subunits but also the editing status of those transcripts [43, 44 and see below].

Several biophysical features have also been ascribed to kainate receptor-mediated responses. These include rates of activation and desensitization, conductance levels and current-voltage relationships (including calcium permeability).

Activation and desensitization

A common characteristic of recombinant kainate receptor kinetics is an observed fast onset of activation and desensitization. Measurements of agonist activation have generally been limited due to technical issues associated with agonist application rates. However, the observed decline in the current magnitude of a response (desensitization) at recombinant kainate receptors using rapid perfusion of GluR transfected cells has been investigated. Thus, for homomeric GluR6(Q) or GluR6(R) and the combination of GluR6(Q)/KA-2, responses are rapid and completely desensitize in less than 30 ms [19]. In contrast, homomeric GluR5(Q) receptor currents are relatively slowly desensitizing, with an estimated τ_1 of 15 ms and a τ_2 of 281 ms [19, 24]. GluR5(Q)/KA2 produces desensitizing current responses with a slower second component of desensitization than that observed with homomeric GluR5(Q) ($\tau_1 = 15$ ms, $\tau_2 + 688$ ms). GluR5(R) produced only very small responses in homomeric forms [37], and the GluR5(R)/KA2 combination produces currents with an initial desensitizing component and a more sustained second component of desensitization [19] that has been likened to currents observed in trigeminal neurons [44].

Channel conductances

Single-channel properties of recombinant kainate receptors have been compared to properties of neuronal kainate receptors. In neurons, the experimental analysis of the single-channel properties of glutamate receptors

pose greater challenges since multiple channel types give rise to a wide range of single channel conductance levels [45]. Marked differences conductance levels are observed for recombinant receptors comprised of either homomeric GluR5 and GluR6 receptors, for channels composed of heteromerics in combination with KA2 subunits or alterations in the editing status of the receptor subunits [37]. For GluR6(Q) channels, domoate activates channels with conductances of 8, 15 and 25 pS, whereas the edited isoform (GluR6(R)) gave channels with very low channel conductances (225 fS). Heteromeric GluR6(Q)/KA2 gave single-channel properties that could not be distinguished from GluR6(Q) alone. GluR5(Q) receptor channels exhibit three conductance states of 5, 9 and 14 pS. Combinations of GluR5(Q)/KA2 resulted in changes in the kinetic properties of the channel with a shortening of the burst duration of the channel. As with GluR6 kainate receptors, the edited version of GluR5(R) has a very low single-channel conductance level (< 200 fS). However, the heteromeric combinations of GluR5(R) and GluR6(R) with KA2 produce higher conductance channels than the homomeric configuration alone. Similar results were obtained using kainate or glutamate as agonists [46, 47].

Current voltage relationships

RNA editing of the Q/R site described above occurs for GluR5 and GluR6 but not GluR7 kainate receptor subunits. For recombinant homomeric receptors comprised of GluR6(Q) (unedited) subunits, agonist responses result in channels with appreciable calcium permeability and inwardly rectifying current-voltage relationships [24, 40, 35]. Unedited kainate receptors are also blocked by Joro spider toxin, whereas edited versions of these channels show low calcium permeability, linear or outwardly rectifying current-voltage relationships and resistance to blockade by Joro spider toxin [48, 49]. Intracellular polyamines are thought to confer the inward rectification to the I–V curves for unedited versions of these channels [38]. When combinations of edited and unedited subunits are made, e.g. GluR5(Q) with GluR5(R) or GluR6(Q) with GluR6(R), channels result with current-voltage relationships that resemble their homomeric edited (R) counterparts [24, 40].

Intracellular modulation of kainate receptors

Biochemical studies have examined the phosphorylation of GluR6 receptors and correlated this with enhancement of ion channel function by protein kinase A (PKA) [50]. These studies have recently been extended to gain an understanding of how the phosphorylation of GluR6 may alter the function of the channel. Evidence suggests that PKA and calcineurin are able to alter the coupling efficiency of glutamate binding and channel opening (as measured by variance analysis of single-channel properties of GluR6) [47].

A recent study has also suggested a possible metabotropic role for kainate receptors. A rat hippocampal slice preparation has been used to examine the effects of kainate on an inhibitory postsynaptic current (IPSC) in the CA1 region. Results obtained suggest that activation of kainate receptors may trigger second messengers resulting in stimulation of protein kinase C (PKC) and activation of phospholipase C (PLC) [51].

Agonist pharmacology

In addition to the endogenous ligand for kainate receptor, glutamate, several agonists, both naturally occurring and synthetic, ligands have been used to study kainate receptor pharmacology and physiology [52, 53]. Such agonists include kainic acid, domoic acid, (*S*)-5-iodowillardiine, (*S*)-5-trifluoromethylwillardiine, 2*S*,4*R*-4-methylglutamic acid, ATPA and LY339434. Derived from the seaweed *Diginea simplex*, kainic acid is a neuroexcitant and excitotoxin that has been widely used as a research tool [54]. Domoic acid is also a potent neurotoxin and originates from the seaweed *Chondria armate*, the same family of algae as *Diginea simplex*. Both kainic acid and domoic acid produce desensitizing responses when applied to kainate receptors. However, the utility of kainic acid as a selective kainate receptor agonist has been somewhat limited since it evokes nondesensitizing responses at AMPA receptors. Although domoic acid is approximately 10-fold more potent than kainate in eliciting responses at GluR5 and GluR6 kainate receptors, it also produces nondesensitizing responses at AMPA receptors and therefore is no more a selective agonist than kainic acid. Interestingly, coexpression of kainate-binding proteins KA1 or KA2 with GluR6 kainate receptors increases sensitivity of kainate receptors to AMPA [55], with a single amino acid (N721 in GluR6) appearing to confer both sensitivity to AMPA and the deactivation rate upon application of domoate [56].

A series of compounds, the willardiines and related azawillardiines, have been demonstrated to show potent and, in some cases, subtype selectivity for kainate receptors [57, 58]. In rat dorsal root ganglion (DRG) (thought to be a GluR5-expressing neuron, see below) neurons, the relative potencies of a series of halogenated willardiines have been examined and a rank order of potency established as 5-iodo > kainate > 5-fluor > AMPA. However, in hippocampal neurons expressing AMPA receptors, the rank order of potency was 5-fluor > AMPA > 5-iodo $\gg$ kainate. Thus, 5-iodowillardiine showed approximately a 100-fold selectivity

between DRG neurons and AMPA receptors in hippocampal neurons. In addition, very weak activity at GluR6 kainate receptors for this compound has been reported [58]. A recent study has also established that 5-iodowillardine does not evoke currents from GluR7 kainate receptors [59]. Heteromeric kainate receptors of GluR6 or GluR7 coexpressed with KA2 subunits are weakly activated by 5-iodowillardiine, an effect similar to the conferred sensitivity of the heteromeric to AMPA. It appears that the same single amino acid (N721) is a residue critical for conferring activity to 5-iodowillardiines at GluR5 and GluR6 kainate receptors.

The pharmacological properties of the agonist (2*S*,4*R*)-4-methylglutamate [60] have been studied in a variety of neuronal and nonneuronal preparations. For example, in rat brain membranes (2*S*,4*R*)-4-methylglutamate inhibits ^{3}H kainate binding with an estimated concentration producing 50% inhibition (IC_{50}) value of 32 nM and with lower affinity at NMDA and AMPA sites. (2*S*,4*R*)-4-methylglutamate also binds to kainate receptors likely to be GluR5 and GluR6 receptor subtypes in rat brain membranes [61]. In accordance with these studies, (2*S*,4*R*)-4-methylglutamate shows binding affinity and functional agonist activity for both human GluR5 and GluR6 receptors [62]. Other functional studies have shown that (2*S*,4*R*)-4-methylglutamate evokes nondesensitizing currents in the presence of concanavalin A in rat DRG neurons [62, 63] and cerebellar granule cells [64]. (2*S*,4*R*)-4-Methylglutamate and kainate are both desensitizing agonists at kainate receptors and can act as functional antagonists to subsequent agonist challenges at concentrations much lower than their functional concentration producing 50% of maximal response (EC_{50}) value (e.g. an IC_{50}s of 8 nM and 30 nM and agonist EC_{50}s of 1 μM and 1.8 μM, respectively) [63].

ATPA is a compound synthesized several years ago as a *tert*-butyl analogue of AMPA. [65]. Although it has a much lower intrinsic potency at AMPA receptors than AMPA, it was considered to be of use in behavioural experiments due to purported improved penetration across the blood brain-barrier [66]. Until recently, the glutamate receptor profile of ATPA was unknown. Clarke et al. [67] showed that ATPA showed a relatively low affinity for hGluR1–4 AMPA receptors with K_i values vs. ^{3}H AMPA binding between 6 and 14 μM. ATPA showed no binding affinity for GluR6 or GluR6/KA2 heteromeric kainate receptors but bound with high affinity to GluR5 (K_i value $\sim$4 nM). Furthermore, ATPA evoked inward currents in GluR5-transfected HEK293 cells and rat dorsal root ganglion neurons. More recently, this compound has been radiolabelled and exhibits saturable high-affinity binding at the GluR5 kainate receptor. ^{3}HATPA also showed similar saturable high-affinity binding to membranes from neonatal rats (K_d $\sim$4 nM) [68]. Another *tert*-butyl-substituted AMPA analogue, ATOA, has recently been shown to have partial agonist activity at GluR5 receptors [69]. A γ-substituted glutamate analogue, LY339434, has been shown to have agonist activity at GluR5 kainate receptors (K_i $\sim$15 nM), in contrast to (2*S*,4*R*)-4-methylglutamic acid, which does not appear to discriminate between GluR5 and GluR6 kainate receptors [62]. LY339434 also has very weak activity at AMPA receptors recorded in neurons.

Antagonist pharmacology

Quinoxalinediones such as NBQX, CNQX and DNQX are competitive AMPA receptor antagonists [70], also having affinity for GluR5 and GluR6 (and GluR6 heteromeric) receptors [71]. This affinity is translated into functional antagonist activity at kainate receptors in rat DRG neurons and recombinant kainate receptors [72, 73]. The oxime derivative NS102 is a weak competitive antagonist of kainate receptors [74, 73], with $\sim$10-fold lower potency at neuronal AMPA receptors in cortical neurons. The limited solubility and selectivity for kainate receptors have precluded this compound from being widely utilized in functional studies of kainate receptors. The decahydroisoquinolmes, LY293558, LY296486 and LY382884 have recently been demonstrated to have varying degrees of AMPA receptor activity (LY293558 > LY294486 > LY382884) whilst maintaining functional antagonist activity at GluR5 receptors. In addition, these compounds have no observable affinity for homomeric GluR6 kainate receptors [67, 72, 75, 76].

Comparisons of several compounds with known activity at glutamate receptors have been performed in cortical neurons and sensory neurons [73]. Compounds from the quinoxalinedione family, including CNQX and ACEA-1011, were compared. Although these compounds have weaker activity at kainate receptors in DRG, there appeared to be little selectivity of these compounds over AMPA receptors where blockade was observed at similar potencies.

Allosteric modulation of kainate receptors

As with AMPA receptors, kainate receptors undergo desensitization upon prolonged exposure to agonists. The physiological consequences of this desensitization are not entirely clear, but it has been suggested that desensitization may be involved in limiting the time course of the postsynaptic response to glutamate [77, 78]. Desensitization of glutamate receptors in mammalian neurons has been shown to be blocked by plant lectins such as concanavalin A and wheat germ agglu-

tanin [79, 80]. The action of lectins appears to be via binding to the carbohydrate side chain of the kainate receptor protein [81]. Also revealed was that although N-glycosylation of the receptor was not required for glutamate receptor function per se, it was essential for modulation of channel activity by lectins. Plant lectins such as concanavalin A, succinyl concanavalin A, wheat germ agglutanin and soyabean agglutanin have been studied on homomeric and heteromeric recombinant kainate receptors, and for GluR6 or GluR6/KA2 receptors more pronounced effects of the lectins were observed on homomeric assemblies of the kainate receptor [82]. The lectins so far examined on kainate receptors are exogenous proteins from plants; however, neurons in both the central nervous system and the peripheral nervous system express endogenous lectins [83]. It is a possibility that these endogenous lectins may play a role in regulating kainate receptor function in neurons.

Neuronal kainate receptors

Spinal cord and dorsal root ganglion neurons

Nociceptive information from the periphery to the spinal cord occurs via primary afferents. Within the dorsal root, dorsal root ganglion cell bodies are associated with primary afferents. It was the early work of Agrawal and Evans [84], that identified that C-fibre afferents possess kainate receptors. In DRG neurons, kainate receptors mediate desensitizing responses to L-glutamate [85]. Desensitization of these responses are removed by concanavalin A [85], and weakly antagonized by the noncompetitive AMPA antagonist 2,3 benzodiazepines [86]. The pharmacological desensitization profile of homomeric GluR5 is similar to kainate responses in DRG neurons [34, 59]. Single-channel recordings of DRG kainate currents reveals two single channel conductance levels of 4 and 8 pS. [85]. Although mRNA expression studies suggest that DRG neurons have mRNA for GluR5, GluR7, KA1 and KA2 [87], the conductance levels in DRG neurons are similar to either GluR5(Q) alone or in combination with KA2. However, recent data that has examined the recovery rates from desensitization to *S*-5-iodowillardiine suggest that similarities exist between homomeric GluR5(Q) and DRG neurons, with slower recovery rates being observed for heteromeric GluR5(Q)/KA2 [57, 59].

The AMPA/GluR5 antagonist, LY293558, a compound that has no significant activity at GluR6, blocks responses to kainate in DRG neurons and human homomeric GluR5 kainate receptors [72]. Capsaicin-induced hyperalgesia an allodynia is humans is also prevented by the AMPA/KA antagonist LY293558 [88]. Similar results were obtained with animal studies that demonstrated that formalin-induced behaviours [75] but not acute physiological nociceptive responses [89] are reduced by the GluR5-selective antagonist, LY382884. Recent studies in spinal cord slices have identified kainate receptor-mediated responses (EPSPs) restricted to synapses formed by high threshold nociceptive and thermoceptive afferent fibres. These data support a role for kainate receptors in contributing to processing of nociceptive information from the periphery to the central nervous system [90].

Trigeminal neurons

Recent studies performed on trigeminal neurons dissociated from the trigeminal ganglia have resulted in the identification of kainate receptors that have biophysical properties similar to GluR5 kainate receptors [44]. In addition, using whole-cell patch-clamp electrophysiology coupled to single-cell PCR, the authors addressed whether the GluR5 subunit combined with KA1 or KA2 subunits. Results of these studies suggest it likely that combination of GluR5(R) and KA2 subunits form functional heteromeric channels in these neurons.

Hippocampal neurons

Given the distinct anatomical features of the hippocampus and the research interest in this area of the brain, it is not surprising that the kainate receptors have been extensively studied in this tissue. Although several of the effects of kainate that have been examined in the CNS are likely attributable to affects on AMPA receptors, certain studies have examined the effects of either low concentrations of kainate or the effects of kainate in the presence of AMPA antagonists. Thus, doses of kainate at subthreshold concentrations for activity at AMPA receptors have been shown to produce depolarizations in hippocampal neurons [91, 92]. A recent resurgence of interest in kainate receptors in the hippocampus has led to several published studies in the last 5 years [reviews 93, 94].

In hippocampal neurons cultured from embryonic rats, kainate receptors have been identified in cells lacking AMPA receptors. Based upon antibody studies and single-cell PCR experiments, evidence supported that these receptors were likely to be of the GluR6 subtype [43, 95, 96]. In hippocampal neurons in dissociated cell culture from neonatal rats, properties of kainate receptors appear to differ from properties expected from GluR6 [97]. In a recent pharmacological study of young cultured neurons from embryonic rats, the mixed GluR5/6 agonists [kainate and (2*S*,4*R*)-4-methyl glutamic acid] evoke currents in these neurons whereas GluR5 specific agonists, such as LY339434 and ATPA, were without effect [71]. Additional evidence for the

absence of a GluR5-mediated current in these neurons came from the lack of antagonism of the agonist responses by the GluR5 antagonists LY294486 and LY382884 [71]. Expression of functional kainate receptor subtypes in these studies could arise through differences in the age of animal from which the tissue was derived or methodological approaches adopted (e.g. culture vs. isolated cells).

In the CA3 region of the hippocampus, pyramidal neurons receive excitatory inputs from mossy fibres. This is one of the first regions in slices to be shown to have kainate receptors involved in synaptic transmission [98, 99]. In these studies, kainate receptors could be activated by high-frequency electrical stimulation of the mossy fibre pathway. This high-frequency stimulation has been suggested to result in spillover of glutamate and an extrasynaptic location of the kainate receptors on the CA3 neurons. Studies in this area of the hippocampus have demonstrated that LY293558 and LY294486, compounds that antagonize GluR5 responses but not GluR6, reversibly antagonize currents induced by kainate postsynaptically on CA3 neurons, suggesting involvement of a GluR5 kainate receptor in this response [100]. Interestingly, the absence of kainate receptor-mediated postsynaptic currents in the CA3 region of GluR6 knockout mice suggests that a heteromeric assembly of GluR5 and GluR6 may contribute to the observed current in this region [101]. A presynaptic role for GluR5 kainate receptors at this mossy fibre/CA3 synapse has also been suggested [102]. The regulation of glutamate release and γ-aminobutyric acid (GABA) release by kainate receptors has been examined in the CA1 region of the hippocampus. Glutamate release from hippocampal synaptosomes is suppressed by kainate following removal of AMPA receptor responses by 2,3 benzodiazepines [103], and synaptic depression was consequently effected by kainate in the Schaffer collateral-commissural CA1 pathway. As with the mossy fibre/CA3 synapse, the CA1/Schaffer collateral commissural synapse appears to have a GluR5 kainate receptor presynaptic component since the depressant effects of kainate are mimicked by the GluR5 agonist ATPA and prevented by the GluR5 antagonist LY294486 [67, 102].

The role of kainate receptors in the modulation of GABA release in the CA1 region of the hippocampus continues to be studied. However, several groups have found differing results. The primary study demonstrating effects of kainate receptor stimulation on GABA-ergic transmission was reported by Clarke et al. [67] and confirmed by Rodriguez-Moreno et al. [104]. Stimulation of GABA-ergic transmission in the CA1 region results in inhibitory postsynaptic potentials (IPSP) that can be recorded in the CA1 neurons. Clarke et al. [67] demonstrated that GABA release could be depressed by a GluR5-selective agonist and that this effect could be reversed by GluR5 antagonists. The kainate-dependent depression of mini IPSP (mIPSP) frequency has also been observed [104, 105]. However, somewhat conflicting results of the presynaptic inhibitory effect of kainate receptors at GABA terminals have been reported. Specifically, Frerking et al. [106] reported that there was no observable effect of kainate on mini-IPSP frequency or on paired-pulse depression of evoked IPSPs, and Cossart et al. [105] reported only modest decreases (25%) in mIPSP frequency.

Cerebellar neurons

Within the cerebellum, kainate receptors have been described on both granule cells and Purkinje cells. In cerebellar granule cell cultures the AMPA/KA receptor antagonist LY293558 blocked kainate receptor-mediated responses [107]. More recently, pharmacological and electrophysiological evidence suggests the involvement of functional kainate receptors that are composed of edited subunits based upon resistance to inhibition by Joro spider toxin [64, 108]. Pemberton et al. [109] have also published electrophysiological evidence for kainate receptors in cerebellar neurons. On the basis of single-cell PCR studies these authors have suggested involvement of GluR6(R) kainate receptors, although rats used in this study were of different ages than those of Savidge and Bristow [108, 109]. Kainate receptors have also been suggested to be present on cerebellar Purkinje neurons from electrophysiological recording of agonist responses in the rat cerebellar slice culture preparation [110].

Amygdala

The involvement of kainate receptors in glutamatergic pathways in the amygdala has recently been investigated [111]. Intracellular recordings of basolateral amygdala neurons in a slice preparation were made and the effects of stimulation of the external capsule examined under conditions where AMPA, NMDA and GABA responses were blocked. Under such conditions a residual current was blocked by both the quinoxalinedione CNQX and the AMPA/kainate antagonist LY293558. Such results suggest an involvement of kainate receptors in synaptic transmission in the amygdala.

Conclusions

The recent resurgence in the interest of researchers in kainate receptors comes over a decade after the initial suggestion of Agrawal and Evans [84] that specific re-

ceptors for kainate existed on dorsal roots of the spinal cord. As we learn more of the molecular biological and biophysical properties of these ligand-gated ion channels and the regional distribution of their proteins, a realization evolves of the their potential functional roles. With recent advances in the development of novel pharmacological tools for kainate receptors, this area of research is set for the dissection of the physiological and pathophysiological roles of kainate receptors in the central nervous system.

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